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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,941	08/24/2001	Robin Thurmond	ORT-1489	2660

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,941	THURMOND ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE filed 6/24 and Amd't filed 3/24 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 24, 2005 has been entered.

Amendment Entry

2. Applicant's amendment and response filed March 24, 2005 is acknowledged and has been entered. Claim 2 has been amended. Currently, claims 2-4 are pending and are under examination.

Rejections Withdrawn

3. All rejections not reiterated herein have been withdrawn.

4. In light of Applicant's amendment and arguments, the rejection of claims 2-4 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. (WO 99/58153) in view of Willman et al. (US Patent 6,495,333).

Chapman et al. disclose monitoring the effect of in vivo administration of cathepsin S inhibitor in a subject (see Abstract and page 14, lines 7-29). According to Chapman et al., dendritic cells or antigen presenting cells express cathepsin S. Chapman et al. specifically teach that by detecting the presence of invariant chain on surface of a dendritic cell or antigen presenting cell using labeled Ii-specific antibody, the effect of in vivo cathepsin S inhibitor to inhibit cathepsin S activity can be monitored

(see page 3, line 32 to page 4, line 4 and lines 14-18, and page 13, lines 16-23). Anti-Ii chain antibodies are used diagnostically in ELISA to evaluate Ii chain expression in vivo (see page 9). Cathepsin S inhibitors include antisense cathepsin nucleic acid molecules and cathepsin inhibitory molecules which are peptides based on vinylsulfone (see page 2, lines 1-10). In practice, Chapman et al. show the effects of cathepsin S inhibitors to Ii degradation by obtaining a cell sample of splenocytes, lysing the cells, then analyzing the lysates for the presence or accumulation of intermediate degradation product of Ii having a 10 kDa fragment, i.e. p10Ii fragment (see Example III, especially, page 17, lines 6-15). In page 13, lines 16-23, Chapman et al. provide a screening assay for determining cathepsin S inhibition by a test compound (cathepsin S inhibitor) using dendritic cells or antigen presenting cells.

Chapman et al. is silent in teaching that the [dendritic] white blood cells are obtained and purified from a blood sample.

Willman et al. disclose that dendritic cells or antigen presenting cells are expressed as white blood T-cells that are rare and are present in peripheral blood samples only in low concentrations (see column 1, line 62 to column 2, line 2). In order to obtain a sample suitable for analysis of cytokines which are antigens present or expressed in dendritic cells, Willman et al. teach purifiying (enriching) and lysing (permeabilizing) the dendritic cells from blood samples in order to isolate and obtain higher concentrations of the cytokines for assay purposes (see Abstract and column 5, lines 7-47).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to purify white blood T-cell samples using the method of Willman to obtain a suitable sample for use in detecting the presence of intermediate degradation product of Ii, i.e. p10Ii, as taught by Chapman, because Willman specifically taught that antigens present or expressed in dendritic cells such as cytokines or intermediate degradation product of Ii can better be detected by first enriching the T-cell concentration so as to isolate increased concentrations of the desired expressed antigen in the sample and so as to be suitable for analytical assays. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the enrichment method of purifying samples as taught by Williams into the method of Chapman because Williams recognized the difficulty in studying intracellular antigens expressed from dendritic cells such as cytokines and pli10 fragments, because of their rarity in peripheral blood samples, but showed that ease in collection of blood as opposed to lymphatic tissue and enrichment of the desired T-cells using positive cell selection thereof, achieves the goal of obtaining adequate concentrations of desired antigens even from rare cell types in peripheral blood sources, as well as practice of less invasive procedures ,i.e. splenectomy, in monitoring compound activity, i.e. cathepsin S inhibition, for pharmaceutical evaluation studies of autoimmune disorders in humans, such as in the taught in the method of Chapman.

Response to Arguments

6. Applicant's arguments filed March 24, 2005 have been fully considered but they are not persuasive.

A) Applicant argues that the combination of Chapman et al. with Willman et al. is in error, does not render obvious the claimed invention and without hindsight knowledge of the present invention, the artisan would have lacked motivation to modify Chapman's methods to analyze whole cell lysates of purified white blood cells from a blood sample for the presence of the p10li fragment as in the claimed invention. Applicant specifically contends that the Willman reference discloses flow cytometric method for measuring dendritic cell function in whole blood, not for method for monitoring the effect in vivo of a cathepsin S inhibitor administered to a subject, let alone of detecting p10li fragment. Applicant argues that Chapman et al. and Willman et al. are for distinct type assays, hence, they cannot be combined.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, Chapman et al. disclose monitoring the effect of in vivo administration of cathepsin S inhibitor in a subject by obtaining a cell sample of splenocytes, lysing the cells, then analyzing the lysates for the presence or

accumulation of intermediate degradation product of Ii having a 10 kDa fragment, i.e. p10Ii fragment. Chapman et al. further provide that dendritic cells or antigen presenting cells express cathepsin S and by detecting the presence of invariant chain on surface of dendritic cells or antigen presenting cells using labeled Ii-specific antibody, the effect of in vivo cathepsin S inhibitor to inhibit cathepsin S activity can be monitored. Willman et al. is incorporated herein, only for the teaching that rare white blood T-cells or dendritic cells from blood samples can be purified and lysed so as to isolate antigens present or expressed in the cells, i.e. cytokines and p10Ii fragment, and obtain a suitable sample for use in analytical assays. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to purify white blood T-cell samples using the method of Willman to obtain a suitable sample for use in detecting the presence of intermediate degradation product of Ii, i.e. p10Ii, as taught by Chapman, because Willman specifically taught that antigens present or expressed in dendritic cells such as cytokines or intermediate degradation product of Ii can better be detected by first enriching the T-cell concentration so as to isolate increased concentrations of the desired expressed antigen in the sample and so as to be suitable for analytical assays. The motivation to do such combination is in the ease in collection of blood as opposed to lymphatic tissue and enrichment of the desired T-cells using positive cell selection thereof which achieves the goal of obtaining adequate concentrations of desired antigens even from rare cell types in peripheral blood sources, as well as practice of less invasive procedures in monitoring compound activity, for pharmaceutical evaluation studies of immune disorders in humans.

In response to applicant's arguments against the Willman reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the rejection is based on the combined teaching of Chapman with Willman as discussed supra. If Willman would have disclosed a method of monitoring the effect in vivo of a cathepsin S inhibitor administered to a subject, by detecting for the presence of p10li fragment in dendritic cells as Applicant suggested to obtain a desired combination, then Willman et al. would have been resolved to an anticipatory rejection.

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status

information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
July 11, 2005